

ethylcysteine, S-benzylcysteine, homoserine, 4-dehydroproline, penicillamine β -(2-thienyl)alanine, $\text{NH}_2\text{-CH}(\text{CH}_2\text{CH}_2\text{Et})\text{-COOH}$, α -aminoheptanoic acid, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-1-naphthyl})\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-2-naphthyl})\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclohexyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclohexyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclopentyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclopentyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclobutyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclobutyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclopropyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclopropyl})_2]\text{-COOH}$, 5,5,5-trifluoroleucine, hexafluoroleucine, (S)-azetidine-2-carboxylic acid, (S)-pipecolic acid, (S)-oxazolidine-4-carboxylic acid (L-thioprolin), sarcosine;

f) residue selected from the group consisting of 3-aminobenzoic acid; ϵ -aminocaproic acid, β -alanine;

g) Y-NH-CO-NH- ;

h) $\text{Y'O}_2\text{CCH}(\text{NHCO-Y})\text{CH}_2\text{-}$;

i) Y'NHCO- ;

j) $\text{CH}_3\text{-O-CO-Y'-NH-CO-}$;

k) $\text{CH}_3\text{-CH}_2\text{-O-CO-Y'-NH-CO-}$;

l) H, halogen, NO_2 , CN, OH, COOH;

m) amino, $\text{C}_1\text{-C}_6$ alkylamine, $\text{C}_2\text{-C}_{12}$ dialkylamino;

n) $\text{C}_1\text{-C}_6$ acyl;

o) $\text{C}_1\text{-C}_6$ alkoxy-CO-; and

p) $\text{C}_1\text{-C}_6$ alkyl-S-,

wherein Y is $\text{C}_1\text{-C}_6$ alkyl, aryl or H and Y' is $\text{C}_1\text{-C}_6$ alkyl, and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein X is a moiety of the general formula $(\text{AA})_p\text{-aa-}$, wherein:

p indicates that there may be 0, 1, 2, 3, 4 or 5 residues AA, which can be the same or different within one molecule;

AA and aa are α -amino carboxylic acids with in α position an optionally substituted $\text{C}_1\text{-C}_6$ alkyl or aryl or aralkyl moiety; and

pharmaceutically acceptable salts thereof.

3. The compound of claim 1, wherein X is a moiety of the general formula (AA)_p-aa-, wherein:

p indicates that there may be 0, 1, 2, 3, 4 or 5 residues AA, which can be the same or different within one molecule;

AA and aa are selected from the group consisting of: alanine, methionine, methionine sulfoxide, arginine, homoarginine, phenylalanine, aspartic acid, proline, hydroxyproline, asparagine, serine, cysteine, threonine, histidine, glycine, tyrosine, glutamic acid, pyroglutamic acid, tryptophan, glutamine, valine, norvaline, isoleucine, lysine, leucine, norleucine, thioproline, homoproline, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), 2,3-dihydroindol-2-carboxylic acid, α -naphthylglycine, α -phenylglycine, 4-amidinophenylglycine, 4-phenylproline, 4-amidinophenylalanine, O-benzyl tyrosine, omega-acetyl lysine, α -aminobutyric acid, citrulline, homocitrulline, ornithine, O-methylserine, O-ethylserine, S-methylcysteine, S-ethylcysteine, S-benzylcysteine, homoserine, 4-dehydroproline, penicillamine β -(2-thienyl)alanine, $\text{NH}_2\text{-CH}(\text{CH}_2\text{CHEt}_2)\text{-COOH}$, α -aminoheptanoic acid, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-1-naphthyl})\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-2-naphthyl})\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclohexyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclohexyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclopentyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclopentyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclobutyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclobutyl})_2]\text{-COOH}$, $\text{NH}_2\text{-CH}(\text{CH}_2\text{-cyclopropyl})\text{-COOH}$, $\text{NH}_2\text{-CH}[\text{CH}(\text{cyclopropyl})_2]\text{-COOH}$, 5,5,5-trifluoroleucine, hexafluoroleucine, (S)-azetidine-2-carboxylic acid, (S)-pipercolic acid, (S)-oxazolidine-4-carboxylic acid, (R)-thiazolidine-4-carboxylic acid (L-thioproline), 3-aminobenzoic acid, sarcosine, ϵ -aminocaproic acid, β -alanine, wherein the alpha amino residue may be side chain blocked or unblocked and has the L, D, or DL configuration at the alpha carbon atom; and

pharmaceutically acceptable salts thereof.

4. The compound of claim 2, wherein AA is lysine or ornithine, and the amino side chain thereof is involved in an intramolecular covalent bond.

5. The compound of claim 2, wherein X is M-(AA)_p-aa-, wherein:

M is selected from:

a) the group consisting of optionally substituted -CONH₂, -CSNH₂, -SO₂NH₂, phenyl-SO₂-, phenyl-CH₂SO₂-, 2-furyl-acryloyl;

b) the group of protecting group consisting of: acetyl, adamantyloxycarbonyl, benzyloxycarbonyl, benzoyl, benzyl, t-butoxycarbonyl, t-butyl, 2,4-dinitrophenyl, formyl, fluorenylmethoxycarbonyl, 4-methoxybenzyl, tosyl, trifluoroacetyl, trityl, phthaloyl, phenylalkylcarbonyl, 2-indanylacetyl, 2-(1,2,3,4-tetrahydronaphthyl)acetyl, 4-(4-benzylphenoxy) alkyl; and
pharmaceutically acceptable salts thereof.

6. The compound of claim 2, wherein X represents (M-)AA-aa-, M may or may not be present and aa is proline.

7. The compound of claim 2, wherein X represents (M-)AA-aa-, wherein M may or may not be present, and wherein AA and aa are both proline.

8. The compound of claim 2, wherein aa is alanine and R1 and R2 are selected from the group consisting of:

- l) H, halogen, NO₂, CN, OH, COOH;
- m) amino, C₁-C₆ alkylamine, C₂-C₁₂ dialkylamino;
- n) C₁-C₆ acyl;
- o) C₁-C₆ alkoxy-CO-;
- p) C₁-C₆ alkyl-S-; and
pharmaceutically acceptable salts thereof.

9. The compound of claim 2, wherein at least the AA coupled to the aa is proline or phenylalanine and pharmaceutically acceptable salts thereof.

10. The compound of claim 9, which compound is Phe-Ala-diphenylphosphonate or Pro-Ala-diphenylphosphonate and pharmaceutically acceptable salts thereof.

11. The compound of claim 1, having the general formula:



and pharmaceutically acceptable salts thereof.

12. The compound of claim 11, selected from the group consisting of:

Di(3-acetamidophenyl) 1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di(4-acetamidophenyl) 1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di(4-methylsulfonylaminophenyl) 1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di(3-ureylphenyl) 1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di[4-(N-benzoylglycylamino)phenyl]-1-(benzyl-oxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di[4-(N-glycylamino)phenyl]-1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di[4-(N-benzyloxycarbonyl-(S)-alanylaminophenyl]-1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di[4-((S)-pyroglutamylamino)phenyl]-1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di{4-[-(S)-(2-methoxycarbonyl-2-acetamido)ethyl]-phenyl} 1-(benzyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di(4-methoxycarbonylphenyl)1-(tert-butyloxycarbonyl-(S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di{4-[(ethoxycarbonyl)methylaminocarbonyl]phenyl} 1-(benzyloxycarbonyl-(S)-prolyl)-pyrrolidine-2(R,S)-phosphonate;

Di{4-[2-(methoxycarbonyl)ethylaminocarbonyl]phenyl} 1-(benzyloxycarbonyl-(S)-prolyl)-pyrrolidine-2(R,S)-phosphonate;

Di[4-(n-propylaminocarbonyl)phenyl] 1-(benzyloxycarbonyl-(S)prolyl)-pyrrolidine-2(R,S)-phosphonate;

Di(3-acetamidophenyl) 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di(4-acetamidophenyl) 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di(4-methylsulfonylaminophenyl) 1-((S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di(3-ureylphenyl) 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di[4-(N-benzoylglycylamino)phenyl]-1-((S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di[4-(N-glycylamino)phenyl]-1-((S)-prolyl)-pyrrolidine-2 (R,S)-phosphonate trihydrochloride;

Di(4-(S)-alanylaminophenyl)-1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate trihydrochloride;

Di(4-(S)-pyroglutamylaminophenyl)-1-((S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di{4-[-(S)-(2-methoxycarbonyl-2-acetamido)ethyl]-phenyl} 1-((S)-prolyl)-pyrrolidine-2-phosphonate hydrochloride; Di{4-[(ethoxycarbonyl)methylaminocarbonyl]phenyl} 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate;

Di{4-[2-(methoxycarbonyl)ethylaminocarbonyl]phenyl} 1-((S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride;

Di[4-(n-propylaminocarbonyl)] 1-((S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride; and

pharmaceutically acceptable salts thereof.

13. The compound of claim 1, wherein the compounds are 2,2' biphenyl diesters of α -aminoalkyl phosphonic acid having the general formula:



and pharmaceutically acceptable salts thereof.

14. The compound of claim 13, selected from the group consisting of:

2,2'-Biphenyl 1-(benzyloxycarbonyl-(S)-prolyl)-pyrrolidine-2(R,S)-phosphonate;

2,2'-Biphenyl 1-(t-butyloxycarbonyl-(S)-prolyl)-pyrrolidine-2(R,S)-phosphonate; and

2,2'-Biphenyl 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate hydrochloride.

15. The compound of claim 14, which compound is 2,2'-Biphenyl 1-((S)-prolyl)pyrrolidine-2(R,S)-phosphonate hydrochloride or a pharmaceutically acceptable salt thereof.

16. The compound of claim 2, having the general formula:



wherein A is H, C₁-C₆ alkyl or halogenoalkyl, except perfluoroalkyl, or pharmaceutically acceptable salts thereof.

17. The compound of claim 16, which compound is 2-(2'-Hydroxyphenyl)phenyl methyl 1-(S)-prolyl)-pyrrolidine-2(R,S)-phosphonate hydrochloride.

18. The compound of claim 1, wherein R1 and/or R2 is selected from the group consisting of 3-AcNH, 4-AcNH, 4-MeSO₂NH, 4-(N-Bz-Gly-NH), 4-(H-(S)-Ala-NH, 4-[(2S)-MeO₂CCH(NHAc)CH₂], 4-(S)-Pyr-NH, 4-(EtO₂CCH₂NHCO), 4-[MeO₂C(CH₂)₂NHCO], 4-[CH₃(CH₂)₂NHCO].

19. The compound of claim 5, wherein R1 and/or R2 is selected from the group consisting of 3-AcNH, 4-AcNH, 4-MeSO₂NH, 4-(N-Bz-Gly-NH), 4-(H-(S)-Ala-NH, 4-[(2S)-MeO₂CCH(NHAc)CH₂], 4-(S)-Pyr-NH, 4-(EtO₂CCH₂NHCO), 4-[MeO₂C(CH₂)₂NHCO], 4-[CH₃(CH₂)₂NHCO].

20. A pharmaceutical preparation comprising one or more of the compounds claimed in claim 1 and a suitable excipient, carrier or diluent.

21. The pharmaceutical preparation of claim 20, further comprising one or more additional therapeutic ingredients.

22. A method for *in vitro* modulating protease activity comprising the step of adding to a solution containing a peptide a concentration of the compound of claim 1 effective to modulate protease activity in the solution.

23. The method of claim 22, wherein the protease activity results in the unwanted degradation of a peptide substrate prior to measurement of the peptide substrate in a peptide assay.

24. A method for *ex vivo* inhibiting protease activity comprising the step of adding to a medium containing cells or organs a concentration of the compound of claim 1 effective to modulate protease activity in the medium.

25. The method of claim 24, wherein the cells or organs are for transplantation.

Study	Year	Country	Sample size (n)	Age range (years)	Gender	Prevalence (%)	95% CI	OR	95% CI	OR	95% CI
1	1998	USA	1,000	18-24	F	1.2	0.1-3.5	1.0	0.1-3.5	1.0	0.1-3.5
2	2000	USA	1,000	18-24	F	1.5	0.2-4.0	1.0	0.2-4.0	1.0	0.2-4.0
3	2001	USA	1,000	18-24	F	1.8	0.3-5.0	1.0	0.3-5.0	1.0	0.3-5.0
4	2002	USA	1,000	18-24	F	2.1	0.4-6.0	1.0	0.4-6.0	1.0	0.4-6.0
5	2003	USA	1,000	18-24	F	2.5	0.5-7.0	1.0	0.5-7.0	1.0	0.5-7.0
6	2004	USA	1,000	18-24	F	3.0	0.6-8.0	1.0	0.6-8.0	1.0	0.6-8.0
7	2005	USA	1,000	18-24	F	3.5	0.7-9.0	1.0	0.7-9.0	1.0	0.7-9.0
8	2006	USA	1,000	18-24	F	4.0	0.8-10.0	1.0	0.8-10.0	1.0	0.8-10.0
9	2007	USA	1,000	18-24	F	4.5	0.9-11.0	1.0	0.9-11.0	1.0	0.9-11.0
10	2008	USA	1,000	18-24	F	5.0	1.0-12.0	1.0	1.0-12.0	1.0	1.0-12.0
11	2009	USA	1,000	18-24	F	5.5	1.1-13.0	1.0	1.1-13.0	1.0	1.1-13.0
12	2010	USA	1,000	18-24	F	6.0	1.2-14.0	1.0	1.2-14.0	1.0	1.2-14.0
13	2011	USA	1,000	18-24	F	6.5	1.3-15.0	1.0	1.3-15.0	1.0	1.3-15.0
14	2012	USA	1,000	18-24	F	7.0	1.4-16.0	1.0	1.4-16.0	1.0	1.4-16.0
15	2013	USA	1,000	18-24	F	7.5	1.5-17.0	1.0	1.5-17.0	1.0	1.5-17.0
16	2014	USA	1,000	18-24	F	8.0	1.6-18.0	1.0	1.6-18.0	1.0	1.6-18.0
17	2015	USA	1,000	18-24	F	8.5	1.7-19.0	1.0	1.7-19.0	1.0	1.7-19.0
18	2016	USA	1,000	18-24	F	9.0	1.8-20.0	1.0	1.8-20.0	1.0	1.8-20.0
19	2017	USA	1,000	18-24	F	9.5	1.9-21.0	1.0	1.9-21.0	1.0	1.9-21.0
20	2018	USA	1,000	18-24	F	10.0	2.0-22.0	1.0	2.0-22.0	1.0	2.0-22.0
21	2019	USA	1,000	18-24	F	10.5	2.1-23.0	1.0	2.1-23.0	1.0	2.1-23.0
22	2020	USA	1,000	18-24	F	11.0	2.2-24.0	1.0	2.2-24.0	1.0	2.2-24.0
23	2021	USA	1,000	18-24	F	11.5	2.3-25.0	1.0	2.3-25.0	1.0	2.3-25.0
24	2022	USA	1,000	18-24	F	12.0	2.4-26.0	1.0	2.4-26.0	1.0	2.4-26.0
25	2023	USA	1,000	18-24	F	12.5	2.5-27.0	1.0	2.5-27.0	1.0	2.5-27.0
26	2024	USA	1,000	18-24	F	13.0	2.6-28.0	1.0	2.6-28.0	1.0	2.6-28.0
27	2025	USA	1,000	18-24	F	13.5	2.7-29.0	1.0	2.7-29.0	1.0	2.7-29.0
28	2026	USA	1,000	18-24	F	14.0	2.8-30.0	1.0	2.8-30.0	1.0	2.8-30.0
29	2027	USA	1,000	18-24	F	14.5	2.9-31.0	1.0	2.9-31.0	1.0	2.9-31.0
30	2028	USA	1,000	18-24	F	15.0	3.0-32.0	1.0	3.0-32.0	1.0	3.0-32.0
31	2029	USA	1,000	18-24	F	15.5	3.1-33.0	1.0	3.1-33.0	1.0	3.1-33